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EXAMINER	
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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/562,803	GAO ET AL.
	Examiner	Art Unit
	NARAYAN K. BHAT	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,9,22,24,26,28,30,31,37,41-43,46,49,53,57-61 and 65-76* is/are pending in the application.

4a) Of the above claim(s) *65-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,9,22,24,26,28,30,31,37,41-43,46,49,53 and 57-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

FINAL ACTION

1. This office action is written in reply to applicant's correspondence filed April 14, 2008. Claim 1 was amended and claim 47 was cancelled. Applicant's amendment requiring “variations in the length and sequence of the immobilized multiple positive control probes, when hybridized with the target nucleotide sequence or the another nucleotide sequence in the preparation create a group of hybridization signals having strong-to-weak or weak-to-strong orderly magnitude” necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**.

2. Claims 1-4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-61 and 65-76 are pending in this application.

3. Claims 1-4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53 and 57-61 are under prosecution.

Specification

4. Objections to the specification in the previous action have been withdrawn in view of submission of SEQ ID Numbers in the CRF and in text format.

Substitute Sequence Listing

5. Substitute sequences listing to correct the inadvertent omission of number of sequences from the previously filed sequence listing has been entered as they don’t

add new matter and to make them compliant with 37 C.F.R. §l.821(c) and §1.8215(a) and (b).

Amendments to Claims

6. Amendments to the claim 1 have been reviewed and entered.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a new rejection necessitated by the claim amendments.

8. Claims 1-4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53 and 57-61 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 1 recites the limitation "the variations in length and sequences of the immobilized positive control probes" in lines 13-14. There is insufficient antecedent basis for this limitation in the claim.

10. Claims 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53 and 57-61 are indefinite because they are dependent from claim 1.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following are new rejections necessitated by the claim amendments.

13. Claims 1, 3-4, 9, 22, 24, 26, 28, 30-31, 37, 43, 46, 49, 53 and 57-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5,567,809 issued Oct. 22, 1996) and Samartziduo et al (Life science news, 2001, 8, 1-3) and Trau et al (Anal. Chem. 2002, 74, 3168-3173) in view of Stockton et al (USPGPUB NO. 2002/01875505 published Dec. 12, 2002).

Regarding claim 1, Apple et al teaches a method of HLA DR beta DNA (DRB) typing comprising isolating the target nucleic acids from cell lines and further teaches

using genomic DNA that contains other genes not related to HLA DR beta (Example 7, column 41, lines 23-27, step ‘a’ of the claim).

Apple et al also teaches a reverse dot blot, (i.e., a chip) comprising a membrane support suitable for use in nucleic acid hybridization having immobilized thereon an oligonucleotide probe complementary to DRB target nucleotide sequence (Example 8, column 43, lines 35-60). Apple et al further teaches that the chip contains probes specific for particular allele type and additionally contains a control probe that detects all of the alleles (column 53, lines 50-67, column 54, lines 15-30 and column 56, lines 33-41). The control probe of Apple et al is the positive control probe as defined in the instant specification (instant specification, USPGPUB, paragraph 0027) and also because it detects all of the DRB alleles (column 56, lines 33-41). Apple et al also teaches that positive control probe create a hybridization signal having intensity equal or less than the positive dots on the chip and provides a guide as to the minimum dot intensity that should be scored as a positive (column 56, lines 36-41). Apple et al are silent about a negative control probe, hybridization control probe an immobilization control probe and multiple positive control probes with length and sequence variations.

Apple et al further teaches hybridizing the array and assessing hybridization between said target nucleotide sequence and/or said another nucleotide sequence and said probes comprised on said chip to determine the type of DRB target gene (Figs 10-13, column 56, lines 42-48).

Regarding claim 3, Apple et al teaches that the target gene is DR beta DNA (DRB), i.e., human leukocyte antigen HLA (column 3, lines 51-60)

Regarding claim 4, Apple et al teaches that the suitable sample is a human bladder tissue that comprises human nucleic acid (column 42, lines 46-54).

Regarding claim 9, Apple et al teaches that the preparation of the target nucleotide sequence comprises a nucleic acid amplification step (column 3, lines 62-65).

Regarding claim 22, Apple et al teaches that the target nucleotide sequence is amplified by PCR using biotinylated primer for hybridization and detection by SA-HRP (column 43, lines 40-48) thus teaching DNA is single stranded at the time of hybridization.

Regarding claim 24, Apple et al teaches that a labeled biotinylated target nucleotide sequence is obtained (column 43, lines 40-48).

Regarding claim 28, Apple et al teaches that the probes are tiled with poly dT to attach the probe to the membrane, thus teaching probe comprised on the chip are modified (column 43, lines 54-60).

Regarding claim 30, Apple et al teaches 22 different DRB probes fixed on the membrane, i.e., chip that meets the limitation of the chip comprises 1-400 different types of probes (Examples 8 and 9, columns 53 and 54 and lines 50-67 and 15-38).

Regarding claim 31, Apple et al teaches two panels of probes containing 11 different DRB probes fixed on the membrane, i.e., chip and further teaches one panel for hybridizing with the DRB amplification products (Example 9, column 53, lines 51-67) and the other with the DRB1-specific amplification products (Example 9, column 54,

lines 15-38) thus teaching multiple arrays of probes and each array comprises 11 probes that meets the limitation of each array comprises 1-400 different types of probes.

Regarding claim 37, Apple et al teaches that 5 to 10 picomoles of the probes, i.e., multiple copies of a probe is immobilized on the chip (column 44, lines 31-35).

Regarding claim 49, Apple et al teaches hybridization solution comprises SSPE and SDS, i.e., surfactant (column 44, lines 52-55).

Regarding claim 53, Apple et al teaches that the hybridization reaction is conducted at a temperature of 50 C which is about 42.C to about 70C (column 44, line 52).

Regarding claim 61, Apple et al teaches that the oligonucleotide probe is complementary to a target HLA gene (column 53, lines 18-25).

Apple et al are silent about a negative control probe, hybridization control probe an immobilization control probe and multiple positive control probes with length and sequence variations. However, a negative control probe and a hybridization control probe were known in the art before the invention was made as taught by Samartziduo et al, who teaches microarray scorecard controls on the chip that includes positive, negative hybridization control probes and probes for dynamic range and ratio controls (Fig. 1, # 2, pg. 1, column 2, paragraph 3). Samartziduo et al further teaches that hybridization controls make a powerful tool for validation of microarray experiments, allowing assessment of target attachment, hybridization uniformity, detection limits, dynamic range and expression ratio (pg. 2, column 1, paragraph 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA typing method of Apple et al and include the hybridization control probe and negative control probe of Samartziduo et al with a reasonable expectation of success.

An artisan would be motivated to modify the HLA typing method of Apple et al and include the hybridization control probe and negative control probe of Samartziduo et al the expected benefit of using a better controls for validation of microarray experiments, allowing assessment of target attachment, hybridization uniformity, detection limits, dynamic range and expression ratio as taught by Samartziduo et al (pg. 2, column 1, paragraph 1) thus having additional control in the HLA typing method of Apple et al.

Apple et al and Samartziduo et al are silent an immobilization control probe. However, an immobilization control probe was known in the art at the time of the invention was made as taught by Trau et al, who teaches an immobilization control probe on the chip (pg. 3169, column 2, paragraph 3, Table 1, Fig. 4 A-D, lane 7). Trau et al further teaches improving quantitative microarray data by normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization (pg. 3173, column 1, paragraph 1)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA typing and data analysis of Apple et al

and Samartziduo et al and to include an additional immobilization control probe and hybridization analysis method of Trau et al with a reasonable expectation of success.

An artisan would be motivated to modify the HLA typing and data analysis of Apple et al and Samartziduo et al and to include an additional immobilization control probe and hybridization analysis method of Trau et al with the expected benefit of improving quantitative microarray data by normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization as taught by Trau et al (pg. 3173, column 1, paragraph 1) thus improving the HLA typing method of Apple et al and Samartziduo et al.

Apple et al and Samartziduo et al and Trau et al are silent about multiple positive control probes with length and sequence variations. However, multiple positive control probes with length and sequence variations were known in the art at the time of the claimed invention was made as taught by Stockton, who teaches genotyping method comprising a plurality of positive control oligonucleotides to which the nucleic acid of interest hybridizes and a plurality of negative control oligonucleotides to which nucleic acid of interest do not hybridize (paragraphs 0043 and 0044). Stockton also teaches that positive control oligonucleotides further comprise a first positive control oligonucleotide containing first boundary sequence without nucleic acid marker and without second boundary sequence, a second positive control oligonucleotide containing second boundary sequence without nucleic acid marker and without first boundary sequence, the third positive control oligonucleotide containing the first

boundary sequence and N+A repeats of the nucleic acid element without the second boundary sequence (paragraph 0045). Stockton further teaches nucleic acid repeat elements are short repeat sequences comprising 2 to 10bases in length (paragraphs 0017-0018). Stockton also teaches that positive control oligonucleotide further comprises an oligonucleotide containing just the nucleic acid marker (e.g., repeats of the nucleic acid sequence elements (paragraph 0043). Teachings of Stockton thus provide multiple positive control probes on the chip having variations in length and sequences as claimed.

Stockton also teaches the positive control oligonucleotide containing the nucleic acid marker without a first or a second boundary sequences always gives the positive signal (paragraph 0043). Stockton further teaches that positive control oligonucleotides containing N+A repeats less than nucleic acid to be detected gives negative signal (paragraph 0043). Combined teachings of Stockton of positive and negative signal from the positive control oligonucleotides meet the limitation of creating a group of hybridization signals having strong to weak orderly magnitude.

Regarding claim 26, Stockton teaches that another nucleotide sequence is complementary to the positive control probe comprised on the chip (paragraph 0044).

Stockton teaches that arrays containing multiple positive control oligonucleotides with variations in length and sequences are very useful in identifying micro deletions, short sequence repeat polymorphism, SNP, allele specific polymorphism and variable tandem repeat polymorphisms and detection of mutations associated with cystic fibrosis (paragraphs 0014 and 0062-0063).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA typing and data analysis of Apple et al, Samartziduo et al and Trau et al and to include multiple positive control with variations in length and sequences of Stockton with a reasonable expectation of success.

An artisan would be motivated to modify the HLA typing and data analysis of Apple et al, Samartziduo et al and Trau et al and to include multiple positive control with variations in length and sequences of Stockton with the expected benefit of having multiple positive control oligonucleotides with variations in length and sequences, which are very useful in identifying micro deletions, short sequence repeat polymorphism, SNP, allele specific polymorphism and variable tandem repeat polymorphisms and detection of mutations associated with cystic fibrosis as taught by Stockton (paragraphs 0014 and 0062-000063), thus increasing the capabilities of the HLA typing method of Apple et al and Samartziduo et al and Trau et al.

Claim 43 is dependent from claim 1. Teachings of Apple et al and Samartziduo et al, Trau et al and Stockton regarding claim 1 are described previously in this office action.

Regarding claim 43, Apple et al and Samartziduo et al, Trau et al and Stockton are silent about hybridization control probe is complementary to a synthetic nucleotide sequence not related to the target gene. However, hybridization control probe is complementary to a synthetic nucleotide sequence not related to the target gene was known in the art before the invention was made as taught by Samartziduo et al, who teaches microarray scorecard controls on the chip that includes positive, negative

hybridization control probes and probes for dynamic range and ratio controls (Fig. 1, # 2, pg. 1, column 2, paragraph 3) and further teaches that these controls are YIR artificial genes and do not hybridize to human or mouse genes and the they are added as controls for hybridization (Table 1, pg. 1, column 2, paragraphs 3 and 4). Samartziduo et al further teaches that hybridization controls make a powerful tool for validation of microarray experiments, allowing assessment of target attachment, hybridization uniformity, detection limits, dynamic range and expression ratio (pg. 2, column 1, paragraph 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA typing method of Apple et al, Samartziduo et al, Trau et al and Stockton and include the hybridization control probe of Samartziduo et al with a reasonable expectation of success.

An artisan would be motivated to modify the HLA typing method of Apple et al, Samartziduo et al, Trau et al and Stockton and include the hybridization control probe of Samartziduo et al with the expected benefit of using a better controls for validation of microarray experiments, allowing assessment of target attachment, hybridization uniformity, detection limits, dynamic range and expression ratio as taught by Samartziduo et al (pg. 2, column 1, paragraph 1), thus having additional control in the HLA typing method of Samartziduo et al, Trau et al and Stockton.

Regarding claims 46 and 57 Samartziduo et al, Trau et al and Stockton are silent about the immobilization control probe and assessing the efficiency of immobilization probe. However, the immobilization control probe and assessing the efficiency of

immobilization probe was known in the art at the time of the invention was made as taught by Trau et al, who teaches an immobilization control probe on the chip (pg. 3169, column 2, paragraph 3, Table 1, Fig. 4 A-D, lane 7) and further teaches that the immobilization control probe is chemically modified at the 5' end (Table 1) and the other end of the immobilization control probe has a detectable Texas red label (Table 1, limitation of claim 46). Trau et al further teaches that the immobilization efficiency is assessed by analyzing a signal from the immobilization control probe (pg. 3171, column 2, paragraph 2, Fig. 4, see the legend for details, limitation of claim 57). Trau et al further teaches improving quantitative microarray data by normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization (pg. 3173, column 1, paragraph 1)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA typing and data analysis of Samartziduo et al, Trau et al and Stockton and include additional immobilization control probe and hybridization analysis method of Trau et al with a reasonable expectation of success.

An artisan would be motivated modify the HLA typing and data analysis of Samartziduo et al, Trau et al and Stockton and include additional immobilization control probe and hybridization analysis method of Trau et al with the expected benefit of improving quantitative microarray data by normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization as taught by Trau et al (pg. 3173, column

1, paragraph 1) thus improving the HLA typing method of Apple et al, Samartziduo et al, Trau et al and Stockton.

Regarding claims 58-60, Apple et al teaches positive control probe, which detects all of the DRB alleles and further teaches the positive control probe provides guidance to score individual DRB allele either positive or negative based on the intensity of the spot relative to the positive control probe (column 56, lines 33-41) thus teaching criteria for hybridization specificity for the closely related HLA DRB probes on the chip (columns 53 and 54, lines 50-67 and 15-30, limitation of claim 60). Apple et al, Samartziduo et al, Trau et al and Stockton are silent about labeled synthetic probe (claim 58) and the ratio between the hybridization signal involving the positive hybridization control probe and the hybridization signal involving the negative hybridization control probe (claim 59) and criteria for determining the positive signals (claim 60). However determining the ratio of signal intensities and establishing criteria for the positive signal for the closely related probes were known in the art at the time of the invention was made as taught by Trau et al, who teaches an array of closely related genes from medicinal plants (pg. 3170, column 2, paragraph 2) and teaches explicitly probes for five different genes (PP, DI, AM, TG and HF) and an immobilization control (Fig. 4, Table 1). Since there is no limiting definition for synthetic nucleotide sequence, the immobilization control probe, which is labeled, is the synthetic nucleotide probe (Trau et al, Table 1) and the probe for PP gene is the hybridization control probe. Trau et al also teaches the analysis of the hybridization of the immobilization control probe and the PP probe (Fig. 4A, limitation of claim 58) thus providing the assessment of

hybridization efficiency between hybridization control probe and the synthetic nucleotide.

Trau et al further teaches the hybridization of PP sample to PP probe (Fig. 4A, column 2) and AM probe (Fig. 4A, column 3), which is a negative control probe, and meets the requirement as defined in the instant specification (Instant specification, paragraph 0027 as per PGPUB) because it comprises multiple base pair changes compared to PP probe (Table 1). Trau et al teaches the ratio of hybridization signal (specific hybridization, Fig. 4A, column 2) to noise (background, Fig. 4A, columns 1 and 8 no probes) is greater than 150 compared to the ratio of hybridization signal (specific hybridization) to noise (unspecific hybridization with AM probe in Fig. 4A, column 3) is greater than 80 (pg, 3172, column 1, paragraph 1) thus teaching the increased ratio between the hybridization signal involving the positive hybridization control probe and the hybridization signal involving the negative hybridization control probe (limitation of claim 59).

Trau et al also teaches an embodiment, wherein the ratio of hybridization signal (specific hybridization, Fig. 4B, column 6) to noise (background, Fig. 4A, columns 1 and 8 no probes) is greater than 150 (pg, 3172, column 1, paragraph 1, limitation of claim 60, step ‘a’) and further teaches the signal to noise ratio range from 150 to 4 (Fig. 4C, column 6) to 2 (Fig. 4D, column 6) thus teaching a range of the ratio of hybridization signal (pg, 3172, column 1, paragraph 1, limitation of claim 60, step ‘b’) and further teaches comparing the hybridization signal of all probes giving positive signals (Fig. 4A, limitation of claim 60, step ‘c’) and two positive signals (probe PP and DI) of closely

related genes (Fig. 4 A and B, limitation of claim 60, step ‘d’). Trau et al also teaches further improvement in quantifying microarray data at a signal to noise ratio of 2, by adjusting template concentration for hybridization and normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization (Fig. 5, pgs. 3172 and 3173, column 1, paragraph 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the array preparation and data analysis of Apple et al, Samartziduo et al, Trau et al and Stockton and include additional immobilization control probe and hybridization analysis method of Trau et al with a reasonable expectation of success.

An artisan would be motivated to modify the array preparation and data analysis of Apple et al, Samartziduo et al, Trau et al and Stockton and include additional immobilization control probe and hybridization analysis method of Trau et al with the expected benefit of improving quantifying microarray data at a signal to noise ratio of 2, by adjusting template concentration for hybridization and normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization as taught by Trau et al (Fig. 5, pgs. 3172 and 3173, column 1, paragraph 1).

14. Claims 1, 2 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5,567,809 issued Oct. 22, 1996), Samartziduo et al (Life science news, 2001, 8, 1-3), Trau et al (Anal. Chem. 2002, 74, 3168-3173) in view of

Stockton et al (USPGPUB NO. 2002/01875505 published Dec. 12, 2002) and further in view of Patterson et al (USPN 5,843,640 issued Dec. 1998).

Claims 2 and 7 are dependent from claim 1. Teachings of Apple et al, Samartzidou et al, Trau et al and Stockton regarding claim 1 are described previously in this office action in section 13.

Regarding claims 2 and 7, Apple et al teaches target nucleic acids are obtained from human bladder tissues and cell lines (Example 7, columns 41 and 42, lines 22-30 and 46-54). Apple et al, Samartzidou et al, Trau et al and Stockton are silent about the leukocyte target cell (claim 2) and isolating them using magnetic micro bead (claim 7). However, method of using magnetic micro bead to isolate the cells including leukocytes was known in the art at the time of the invention was made as taught by Patterson et al, who teaches the isolation of lymphocytes from PBMCs using magnetic beads and further teaches that the magnetic bead method provides highly enriched population of CD4 lymphocytes, i. e., leukocytes (column 12, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the target cell isolation method of Apple et al, Samartzidou et al, Trau et al and Stockton and use the magnetic bead method of Patterson et al with a reasonable expectation of success.

An artesian would have motivated to modify the target cell isolation method of Apple et al, Samartzidou et al, Trau et al and Stockton and use the magnetic bead method of Patterson et al with the expected benefit of obtaining highly enriched

population of leukocytes from PBMCs as taught by Patterson et al (column 12, lines 46-50).

15. Claims 1 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5,567,809 issued Oct. 22, 1996), Samartziduo et al (Life science news, 2001, 8, 1-3), Trau et al (Anal. Chem. 2002, 74, 3168-3173) in view of Stockton et al (USPGPUB NO. 2002/01875505 published Dec. 12, 2002) and further in view of Straus (USPGPUB NO. 2002/0086289 published July 4, 2002).

Claim 41 is dependent from claim 1. Teachings of Apple et al, Samartzidou et al, Trau et al and Stockton regarding claim 1 are described previously in this office action in section 13.

Regarding claim 41, Apple et al, Samartzidou et al, Trau et and Stockton teaches contains a control probe that detects all of the HLA alleles (columns 53, 54 and 56, lines 50-67, 15-30 and 33-41). The control probe of Apple et al is the positive control probe as defined in the instant specification (paragraph 0027) and also because it detects all of the DRB alleles (column 56, lines 33-41). Stockton teaches multiple positive control probes with sequence and length variations. Apple et al, Samartzidou et al, Trau et al and Stockton are silent about positive control probe complementarity to a portion of the target nucleotide sequence. However, positive control probe complementary to a portion of the target nucleotide sequence was known in the art at the time of the invention was made as taught by Straus, who teaches a method for genomic profiling, which includes a positive control probe on the chip hybridizes to a target control sequence (paragraphs

191 and 210), which meets the definition of the positive control probe as defined in the instant specification (paragraph 0027, as per USPGPUB). Straus also teaches adding positive control DNA sample to the experimental DNA sample for amplification thus teaching nucleotide sequence amplified synchronically with the experimental sample and further teaches that positive control probes are detected in all assays except for failure of assay steps (paragraph 0210). Straus further teaches failure to detect a signal from positive control probe indicates a false negative result (paragraph 0210).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the target detection method of Apple et al, Samartzidou et al, Trau et and Stockton and include the positive control probe complementary to a portion of target sequence of Straus with a reasonable expectation of success.

An artisan would be motivated modify the target detection method of Apple et al, Samartzidou et al, Trau et al and Stockton and include the positive control probe complementary to a portion of target sequence of Straus with the expected benefit of confirming the false negative result due to failure to detect a signal from positive control probe as taught by Straus (paragraph 0210).

16. Claims 1 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable Apple et al (USPN 5,567,809 issued Oct. 22, 1996), Samartziduo et al (Life science news, 2001, 8, 1-3), Trau et al (Anal. Chem. 2002, 74, 3168-3173), Stockton (USPGPUB NO. 2002/01875505 published Dec. 12, 2002) and Straus (USPGPUB NO.

2002/0086289 published July 4, 2002) and further in view of Delenstarr et al (USPGPUBNO. 2002/0051973 published May 2, 2002).

Claim 42 is dependent from claim 41, which is dependent from claim 1. Teachings of Apple et al, Samartzidou et al, Trau et al, Stockton and Straus regarding claims 1 and 41 are described previously in this office action in 14.

Regarding claim 42, Straus teaches a negative control probe (paragraph 180) but do not teach negative control probe has about 1-3 base pair mismatches compared to positive control probe. However, negative control probe having about 1-3 base pair mismatches compared to positive control probe was in the art at the time of the invention was made as taught by Delenstarr, who teaches a positive control probe (paragraph 0076) and a negative control probe (paragraph 0075). Delenstarr also teaches that negative control probe (paragraphs 151-152, Table 5, SEQ ID NO. 32) has about 3 base pair mismatches when compared to the positive control probe (paragraph 0129, SEQ ID NO. 2). Delenstarr also teaches a method to identify the shortest length of background probes, i.e., negative control probe (Delenstarr et al also refers negative control probe as background probes, paragraph 0075) that mimics the properties of longer probes, yet have reduced affinities for complementary target sequence (paragraph 150).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the negative control probe of Apple et al, Samartzidou et al, Trau et al, Stockton and Straus for the genomic profiling and include

shorter negative control probe of Delenstarr et al with a reasonable expectation of success.

An artisan would be motivated modify the negative control probe of Apple et al, Samartzidou et al, Trau et al, Stockton and Straus for the genomic profiling and include shorter negative control probe of Delenstarr et al with the expected benefit of using a negative control probe of shorter length that mimics longer probe properties, yet having reduced affinity complementary target sequence as taught by Delenstarr et al (paragraph 150).

Response to remarks from the Applicants

Rejections under 35 U.S.C. § 102(b)

17. Applicant's arguments with respect to claims 1, 3-4, 9, 22, 24, 28, 30-31, 37, 49, 53 and 61 as being anticipated by Apple et al have been fully considered but are moot in view of the new grounds of rejection necessitated by the claim amendments (Remarks, pgs. 16-17).

Applicant's arguments with respect to claims 1-2, 4, 9, 22, 24, 26, 41, 43, 49 and 53 as being anticipated by Straus have been fully considered but are moot in view of the new grounds of rejection necessitated by the claim amendments (Remarks, pgs. 17-18).

Rejections under 35 U.S.C. § 103(a)

18. Applicant's arguments with respect to claims 1-2 and 7 as being unpatentable over Apple et al in view of Patterson et al have been fully considered but are moot in

view of new grounds of rejection necessitated by amendments to the claim (Remarks, pgs. 18-20).

In general, Applicants argument on the obviousness rejection is based mainly on the teachings of Apple et al about the controls used in the microarray chip. Applicants argue that “neither Apple et al nor the combination of references used in the previous rejections, viz., Patterson et al, Samartzidou et al, Trau et al, Straus and Delenstarr et al, do not teach the suggests using a chip comprising all four immobilized control probes, or a chip comprising multiple immobilized positive control probes, wherein the variations in the length and sequence of said probes, when hybridized with the target nucleotide sequence or another nucleotide sequence in the preparation, create a group of hybridization signals having strong-to-weak or weak-to-strong orderly magnitude” (Remarks, pg. 20, paragraph 3). These arguments are not persuasive for the following reasons.

a. As described in this office action in detail in section 13, Apple et al teaches a positive control probe immobilized on the chip. Stockton teaches a plurality of positive control sequences comprising different lengths and variation in the sequences. Stockton also teaches creating group of hybridization signals having a very strong to a negative signals using different positive control probes (Stockton, paragraphs 0043-0045). In fact Stockton teaches all the limitations of positive and negative control probes as recited in the amended claim 1. Samartzidou et al teaches positive, hybridization, dynamic range, ratio and negative control probes on the chip for assessing target attachment, hybridization uniformity, detection limits and data normalization (pg. 2, column 1,

paragraph 1). Trau et al teaches immobilization control. Straus teaches positive and negative controls. As described in this office action in detail in sections, 14-17, the controls that Apple et al are silent about are taught by other cited references and provide excellent teachings, suggestions and motivation to combine with the teachings of Apple et al.

b. Applicants have not traversed the teachings, suggestions and motivation provided by the combination references.

c. Applicants have not provided persuasive arguments why one having the skill in the art wouldn't combine the teachings of reference cited in to have a variety of controls on the chip to validate data obtained.

d. Since all the steps recited in claim 1 and dependent claims are taught by the references cited in, Applicant's arguments are not persuasive.

Applicant's arguments regarding claims 1 and 41-42 as being unpatentable over Straus in view of Delanstarr have been fully considered but are moot in view of new grounds of rejection necessitated by amendments to the claim (Remarks, pgs. 21-22). Applicants reiterating arguments over the controls that are not taught by Straus in view of Delanstarr are not persuasive for the same reasons as listed above in section 19, subsection a-d.

Applicant's arguments regarding claims 1 and 43 as being unpatentable over Apple in view of Samartziduo have been fully considered but are moot in view of new grounds of rejection necessitated by amendments to the claim (Remarks, pgs. 22-23). Applicants reiterating arguments over the controls that are not taught by Apple in view

of Samartziduo are not persuasive for the same reasons as listed above in section 19, subsection a-d.

Applicant's arguments regarding claims 1, 46 and 57-60 as being unpatentable over Apple in view of Trau have been fully considered but are moot in view of new grounds of rejection necessitated by amendments to the claim (Remarks, pgs. 23-24). Applicants reiterating arguments over the controls that are not taught by Apple in view of Trau are not persuasive for the same reasons as listed above in section 19, subsection a-d.

Applicant's arguments regarding cancelled claim 47 are moot (Remarks, pg. 24-25).

Conclusion

19. No claims are allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571)-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Narayan K. Bhat/

Examiner, Art Unit 1634

Narayan K. Bhat, Ph. D.

/BJ Forman/

Primary Examiner, Art Unit 1634